

REMARKS

The official action of 12 November 2009 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claim 45 has been amended to make clear that the same solvent system for refinement in step (d) as is used for resolution of (\pm) CPA in step (a) (see specification as filed at, for example, page 2, last paragraph, and page 6, lines 1-4). This overcomes certain drawbacks of the prior art method as discussed below. Certain claims have been canceled to simplify the prosecution and to make room for the addition of new claims (discussed next) without the need to pay excess claim fees.

New claims 82-84 have been added more completely to define the subject matter which Applicants regard as their invention. Support for the recitations in claims 83-84 appears in the specification as filed at, for example, page 6, lines 1-4.

The cancellation of claims 66 and 75 render moot the objections to these claims at paragraph 7 of the official action.

The claims stand rejected under 35 USC 103(a) as allegedly being unpatentable over Masahiro et al in view of Takuma et al and Yoneyoshi et al. Applicants respectfully traverse these rejections.

The claimed invention is directed to a process for the preparation of (+) 2-(4-chorophenyl)-3-methyl butanoic acid (CPA) with a resolving agent comprising an amine in a hydrophobic/hydrophilic organic solvent in the presence of water. The desired amine salt obtained is separated and refined with the same solvent system used for resolution and recovering the desired (+)CPA as well as undesired (-)CPA and an amine resolving agent. The claimed invention involves recovery and recycling of the undesired R-isomer, recovery and recycling of the expensive resolving agent and use of a solvent system wherein the loss of solvent to environment is minimized. The claimed method is carried out in water and

partly/totally miscible organic solvents with the latter being preferably alcohols containing C₃-C₅ carbon units and uses the same solvent system for refining process of diastereomeric salt so as to obtain +(+)CPA with high optical purity.

Advantages of the claimed invention include:

1. The claimed invention makes it possible to obtain high optically pure(+) CPA with a fewer number of refinements (one/two) and utilizes same solvent system as used for resolution of (±) CPA for refinements.
2. The effective recovery of (-)CPA for recycling it after racemization.
3. The recovery of the optically active resolving amine in an effective manner and its recycling to conserve reagent and enhance the cost-effectiveness of the process.
4. The process is comprehensive in that resolving agent, acid and the organic solvent are effectively recovered and recycled thereby reducing the environmental burden.

Masahiro et al. is directed to a method for the optical resolution of (+)CPA with optical purity of +45.93° of (+) CPA acids with a yield of 41.7% based on (±)CPA charged. This reference employs three solvent systems for resolution of (±)CPA and purification of salt is carried out in a different solvent system than used for resolution of acid. An inherent drawback of this reference is that the use of different solvent systems for optical resolution causes cross contamination of the solvents and the separation of the solvents poses environmental and commercial problems.

The claimed invention overcomes these drawbacks by providing a process for the preparation of (+) 2-(4-chlorophenyl)-3-methyl butanoic acid (CPA) which makes it possible to obtain high optically pure (+) CPA with fewer number of refinements (one/two) (see claim 47) and utilizes the same solvent system as used for resolution of (±) CPA for refinements (all claims). Also the claimed process yields not only (+) CPA, it also recovers the (-)CPA to recycle it after racemization (see claim 48). The process is comprehensive in that resolving agent, acid and the organic solvent are effectively recovered and recycled

thereby reducing the environmental burden. The recovery of the optically active resolving amine in an effective manner and its recycling is significant in conserving reagent and enhancing the cost effectiveness of the process from an economic viewpoint.

Masahiro et al. employs a three component system (toluene, methanol and water) whereas in the claimed invention, a solvent system with only two components (an organic solvent and water) is used (see claim 82). Also Masahiro et al do not disclose the use of high alcohols. Moreover, the results provided by the claimed invention could not be obtained under the same experimental conditions as described in Masahiro et al. (see Table 1 of the present specification).

Other patentable distinctions of the claimed invention reside in the process conditions. As acknowledged by the Examiner on pages 3 and 4 of the Office Action, Masahiro et al are silent about cooling the resultant mixture comprising crystallized salt, the concentrations of reactants, temperature range of the reaction conditions, recovering (-) CPA using the solvent system, selected from dichloromethane, dichloroethane, chloroform, toluene and hexane and recovery of resolving agent.

Neither of the cited secondary references can supplement the deficiencies in the primary reference. **Takuma et al** addresses a very specific problem associated with the prior art. This reference finds that, if the starting material is of certain defined purity, then the final product will also be optically very pure. Therefore, according to Takoma et al., the α -phenyl- β -(P-tolyl)ethylamine (PTE) should not be less than 95% optical purity, in order to obtain the desired salt of CPA with amine with desired optical purity. The entire focus in this reference is on the use of an optically pure starting material. There is no guidance or teaching towards the use of the same solvent system or the specific reaction parameters. In addition, Takoma et al rely on the solvent systems and reaction parameters of Masahiro et al. (see page 2, lines 11 to 20). On page 2, lines 11 to 20, Takoma et al. clearly state that the process of Masahiro et al does not provide good filterability of the salt crystal when the (+)-PTE used is of low optical purity.

This reference teaches a process wherein (\pm) CPA is resolved using (+)-PTE in polar solvent or a mixture thereof with a hydrophobic solvent and water and comprises a programmed rate of cooling. The process does not include recovery and recycling of undesired (-)CPA, resolving agent and solvent making it less attractive from an industrial application and economical point of view.

Yoneyoshi et al. also cannot supplement the aforementioned deficiencies of the primary reference. Moreover, Yoneyoshi describes the use of a secondary amine as a resolving agent. The amount of resolving agent in terms of weight (sub-stoichiometric quantity) is lower than the higher quantities (stoichiometric quantity) used in the case of secondary amines. The solvent system of Yoneyoshi is entirely different from that claimed and cannot be combined with the primary reference to arrive at the claimed invention for this reason as well.

Also in the claimed invention, the optical purity is 98% and yield of (+)2-(4-chlorophenyl)-3-methylbutanoic acid (+)CPA is 40% whereas in the reference the optical purity and yield of (+)2-(4-chlorophenyl)-3-methylbutanoic acid (+)CPA is 90% and 31% respectively (see Yoneyoshi at Example 48). Accordingly, one of skill in the art would not combine Yoneyoshi with the other cited references to arrive at the claimed invention.

In short, the problems solved by the claimed invention in obtaining (+)CPA with high yields, in an environmentally friendly manner, by a simpler and less cumbersome process that is more energy efficient and with high optical purity are not addressed by the cited references. To the contrary, these problems are associated with all of the three cited references. These problems have been overcome in the claimed invention with the specific solvent systems and amounts and temperatures and sequence of steps recited in the claims. These features are not shown by the references either alone or in proper combination.

In view of the above, Applicants respectfully submit that all rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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